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Anemia treatment and decline of renal function

To the Editor: In the August issue of *Kidney International* Gouva et al [1] reported a significant benefit in terms of death or aggravation of renal failure in nondiabetic patients with chronic renal failure and anemia randomized to the early, systematic administration of erythropoietin with a target hemoglobin (Hb) concentration of 13 g/dL, compared with deferred treatment started when Hb reached a concentration ≤9 g/dL.

Results of this well-designed study are welcome because they demonstrate a benefit of the correction of anemia in chronic renal failure (CRF) on hard end points (doubling of creatinine or creatinine of >8 mg/dL or initiation of renal replacement or death). This trial raises, however, an ethical issue because American [2] and European [3] guidelines published in 1997 and 1999 recommended in predialysis patients a Hb concentration of 10 and 11 g/dL, respectively, based on evidence of a better quality of life and cardiovascular protection [2, 3]. With a baseline creatinine clearance of 26.7 ± 9.1 mL/min and 22.3 ± 6.0 mL/min in early and deferred treatment arms, respectively, most patients in Gouva's study were in the target of guidelines. Moreover, this study leaves open two important questions: the target Hb concentration and the glomerular filtration rate (GFR) threshold for intervention. It is necessary to determine if an Hb concentration higher than recommended (≥13 g/dL) results in a slower progression of CRF and is well tolerated. We need also to evaluate the effects of correcting anemia earlier in the course of CRF, when GFR is still >25 mL/min and the correction of anemia can be expected to be more effective on CRF progression.

The NEPHRODIAB2 study was designed to answer these questions in type 2 diabetic patients with GFR 25 to 60 mL/min/1.73m^2 and Hb 10 to 12.9 g/dL [4]. In this randomized trial, primary end point is the decline in GFR in normal (11-12.9 g/dL) versus high Hb concentration (13-14.9 g/dL) arms after two years of follow-up. The planned sample size is 204. Inclusions started in France in February 2004.

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Reply from the Authors

We thank Dr. Villar et al for their comments. Most expert guidelines at the time that our study was designed would probably suggest treating anemia for hemoglobin <10 g/dL [1] or even <11 g/dL [2]. However, as these same guidelines had acknowledged up front, "the target hemoglobin concentration perhaps represents the most controversial single issue in the application of epoetin today" [2]. Moreover, most of the available prior evidence pertained to patients with more advanced renal disease than in our study and/or patients with diabetes mellitus. Finally, the outcomes were mostly centered on quality of life, and it is well known that quality of life can be subject to considerable measurement error and bias [3]. Thus, we felt it was a top priority to generate appropriate evidence for the implementation of erythropoietin treatment in patients with modest renal function impairment, rather than perpetuate a debate with limited data. We welcome the interesting NEPHRODIAB2 study that Dr. Villar et al are conducting, and we look forward to seeing their results. We believe that similar studies may need to be conducted also in nondiabetic patients with a similar early level of renal dysfunction. However, studying these patient populations, especially nondiabetic ones, is challenging. Given the early stage of disease, very few disease progression events are likely to occur even with considerable follow-up, and the cost-benefit of chronic